REMARKS/ARGUMENTS

By the present amendment, claim 1 has been amended in order to specify that the composition is delivered to a lysosome in a cell. Support for this amendment can be found throughout the application as filed, for example, on page 4, lines 28-29. Clam 10 has been cancelled and claims 21-29 have been withdrawn as being directed to a non-elected invention.

The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application. No new matter has been entered by the present amendment and its entry is respectfully requested.

The office action dated January 29, 2008 has been carefully considered. It is believed that the amendments and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Restriction/Election

We confirm that Applicant has elected the Group I invention comprising claims 1-20. Consequently, claims 21-29 have been withdrawn. However, we disagree with the Examiner that claims 6 and 15 should be withdrawn as they do not relate to a non-elected invention, but rather a non-elected species. Since the election of a species does not restrict the scope of the claim, claims 6 and 15 have been retained.

Objection to the Specification

The Examiner has objected to page 1 of the specification because it does not cite the application priority date. In response, page 1 has been amended to include the priority data.

Objection to the Claims

Claim 10 is objected to due to a typographical error. Claim 10 has been cancelled by the present amendment which overcomes the objection.

Double Patenting

The Examiner has objected to claims 14-20 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of co-pending U.S. application no. 10/588,425. We respectfully disagree with the Examiner for the reasons that follow.

Current claims 14-20 are directed to a compound comprising a p97 molecule covalently linked to a protein whose deficiency causes a lysosomal storage disease. The co-pending application relates to modified lysosomal enzymes which have been highly phosphorylated. In particular, claims 1 and 2 of the co-pending application describes lysosomal enzymes that have been produced in CHO cells "wherein said enzyme has a high level of phosphorylation and a low level of unphosphorylated high-mannose oligosaccharides". These claims do not relate to enzymes conjugated to p97 and therefore are patentably distinct from the present claims.

In view of the foregoing, we respectfully request that the objection to the claims on the ground of non-statutory obviousness-type double patenting be withdrawn.

35 USC §112

The Examiner has objected to claim 10 under 35 USC §112, second paragraph, as being indefinite. In response, claim 10 has been cancelled which overcomes the objection.

In view of the foregoing, we respectfully request that the objection to the claim under 35 USC §112 be withdrawn.

35 USC §103

The Examiner has objected to claims 1-5, 7-14 and 16-20 under 35 USC §103(a) as obvious over the combined teachings from Neuwelt (U.S. Patent No. 4,866,042) in view of Jefferies et al. (U.S. Patent No. 5,981,194) and WikiPedia Foundation, Inc. (see Sandhoff disease, http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008) and further in view of Lebowitz (USPGPB 2003/0072761 A1). We respectfully disagree with the Examiner for the reasons that follow.

The Supreme Court recently addressed the proper standard for obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). There, the Court held that the proper question for evaluating obviousness is "whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR*, 127 S.Ct. at 1741. The Federal Circuit considered the "reason" requirement in *Takeda Chem. Industs., Ltd. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (2007), reversing an obviousness finding when the claims recited a specific chemical compound and "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." The court emphasized that obviousness requires that the prior art give a reason or motivation to make the specific composition claimed. *Takeda*, 492 F.3d at 1356.

Thus, for a proper combination of references, there must be some indicative teaching or suggestion in the prior art. MPEP § 2142. The mere fact that references can be

combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP § 2143.01.

The cited references together fail to suggest delivering p97-conjugates to a lysosome in a cell. The cited art evidence no motivation to have combined the teachings in question, as asserted, in order to arrive at the claimed invention. Further, no combination of cited references could have provided a reasonable (i.e., a principled) expectation that such combination would result in claimed invention.

The primary reference cited by the Examiner is Neuwelt. Neuwelt is concerned with methods to deliver "genetic material" across the blood brain barrier by chemically altering the blood brain barrier to permit passage of the material. Neuwelt's method is non-specific and allows all components that are normally excluded from the brain by the blood brain barrier to enter. While Neuwelt does disclose using its non-specific method to treat lysosomal storage diseases of the brain, nowhere does Neuwelt disclose or even remotely suggest a method involving coupling the therapeutic agent of interest to p97. Further, Neuwelt provides no teaching or suggestion that p97 could deliver therapeutics directly into a lysosome in a cell. Neuwelt is not concerned with delivery to lysosomes.

The deficiencies in Neuwelt are not remedied by Jefferies et al. Jefferies et al. teaches that p97 can be used to transport therapeutics across the blood brain barrier. Jefferies discloses that such therapeutic agents could be used to treat neurodegenerative diseases or tumors of the brain. Jefferies et al. does not disclose or suggest that p97 could deliver therapeutic agents into a lysosome in a cell. With respect, the Examiner is incorrect in stating that "Jefferies et al. also teach compositions comprising p97 and delivering it to the subject in need thereof to diagnose, monitor and treat a lysosomal storage disease, i.e. Alzheimer's (Column 101, Line 25 to Column 102, Line 2). **Alzheimer's disease is not a lysosomal storage disease.** Further, the reference provided in Jefferies, column 101/102, is directed at claim 6 of the issued patent which relates to a method of diagnosing or monitoring Alzheimer's disease by detecting p97 in a sample from subject.

Based on the combined teachings of Neuwelt and Jefferies et al., one of skill in the art would **not** have a reasonable expectation that p97 could be used to target therapeutic agents to a lysosome. The ability of p97 to transport agents across the blood brain barrier is by transcytosis, wherein the agent is transported across the endothelial cells that form a barrier to a brain. Based on that mechanism of action, one could not predict whether or not p97 could also deliver agents into the lysosomes. In fact, p97 is closely related to transferrin although transferrin transports into the endosomes rather than lysosomes. Further, as the Examiner has not provided a reasonable basis by which the combination of references render the claims obvious, the objection should be removed.

The Examiner also cites LeBowitz and WikiPedia Foundation in support of the objection. However, both of these references are specific references on Sandhoff disease which merely teach that Sandhoff disease is result of the absence or defect in the presence of

β-hexosaminidase. Applicant does not dispute that the deficiency in Sandhoff disease was known in the art and that it would be desirable to provide β-hexosaminidase to a person with Sandhoff disease. However, these references failed to provide any suggestion or motivation to couple the therapeutic enzyme to p97 in order to facilitate transport into the lysosomes. In fact the major issue in treating this disease is that enzymes are not targeted for delivery to the brain for overcoming the neurological effects of the disease. Therefore it is not obvious that p97 can transport enzymes across the blood brain barrier **and** deliver the enzymes to the lysosomes of the affected neurons therein.

In view of the foregoing, we respectfully request that the objection to the claim under 35 USC §103 be withdrawn.

The Commissioner is hereby authorized to charge any fee (including any claim fee) which may be required to our Deposit Account No. 02-2095.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, she is kindly requested to contact the undersigned by telephone at (416) 957-1682 at her convenience.

Respectfully submitted,

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